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Diffuse Plasmacytosis in a Child With Brainstem Glioma Following Multiagent Chemotherapy and Intensive Growth Factor Support

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The use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage–colony-stimulating factor (GM-CSF) in order to abrogate chemotherapy-induced neutropenia has become a routine part of many cancer treatment regimens. However, there are still very few data available about possible complications related to repeated or prolonged use of these agents in patients with malignant solid tumors. The authors report a child with brainstem glioma who received repeated cycles of multiagent chemotherapy with G- or GM-CSF support. During this period of 10 months, no clinical side effects were observed that could have been attributed to growth factor administration. However, postmortem histological examination revealed the presence of diffuse plasmacytosis, a rare hematological disorder in childhood. Undifferentiated plasma cells of nonmonoclonal origin could be demonstrated infiltrating bone marrow, lungs, and lymph nodes of the patient. Based on previously published in vitro and in vivo evidence on the interleukin-6 (IL-6)–mediated stimulatory effect of G- and GM-CSF on myeloma cell proliferation, the authors suggest a possible link between extensive growth factor support and the development of plasmacytosis in this patient.

Key words: plasmacytosis, glioma, chemotherapy, growth factor, GM-CSF, G-CSF

INTRODUCTION

Hematopoietic growth factors or colony-stimulating factors (CSF) are potent regulators of blood cell proliferation and development. They have been introduced into clinical trials in the 1980s to treat several different conditions of primary and secondary bone marrow dysfunction [1]. Encourging results facilitated the widespread clinical use of granulocyte-macrophage–colony-stimulating factor (GM-CSF), granulocyte–colony-stimulating factor (G-CSF), and erythropoietin, mainly in the fields of myelotoxic cancer chemotherapy and bone marrow transplantation [2,3].

Neutropenia and sepsis are major life-threatening and dose-limiting complications of cancer treatment regimens. Therefore, potential benefits of GM-CSF and G-CSF application in cancer chemotherapy are to prevent or to decrease the duration and degree of neutropenic periods after chemotherapy and to allow dose-intensification of anticancer agents [4].

In spite of the fact that some of the performed clinical trials failed to show any clear benefit of CSF administration, their use had become routine in dose-intensive cancer chemotherapy [5,6]. G-CSF and GM-CSF are very well tolerated, and acute clinical side effects, such as bone pain, fever, and myalgia, can be easily managed. Long-term, continuous use of colony-stimulating factors has been reported with no evidence of side effects in patients with chronic neutropenia but has also been associated with an increased risk of developing acute leukemia in patients with myelodysplastic syndrome [8,9]. Based on mainly preclinical data, the problems of tumor growth promotion, lineage competition, and stem cell exhaustion have been discussed extensively in the literature [10]. However, there are still few clinical data available about possible complications related to the repeated or prolonged use of G-CSF and/or GM-CSF in nonhematological diseases, such as, for example, in patients with malignant solid tumors.

Case Report

In July 1992 a 15-year-old white male child presented with symptoms of headaches, diplopia, and gait instabil-

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ity. Magnetic resonance imaging (MRI) examination revealed a large diffuse brainstem tumor, with a size of $5 \times 4 \times 4$ cm, infiltrating major parts of the pons and partially compressing the fourth ventricle. The localization and size of the tumor did not allow a biopsy or surgical resection. Therefore, after the radiological diagnosis of a diffuse brainstem glioma, radiotherapy was started immediately. After completing 5 weeks of radiotherapy (50 Gy conventional boost irradiation of the tumor), a partial response was achieved, with marked improvement of the child's neurological symptoms. In the subsequent period of 10 months (September 1992 to July 1993), the patient was treated with multiagent chemotherapy, including the following cycles:

Cycle 1: Cisplatin 120 mg/m^2 on day 1; VP-16 2×100 mg/m^2 on days 1–2

Cycle 2: Vincristine 2×1.5 mg/m^2 on days 1 and 8; dibromodulcitol 2×500 mg/m^2 on days 1, 8, and 15; procarbazine 15×100 mg/m^2 on days 1–15

Cycle 3: BCNU 2×100 mg/m^2 and ara-C 2×3 g/m^2, both drugs on days 1–2

Cycles 4–7: BCNU 2×100 mg/m^2 and ara-C g/m^2, both drugs on days 1–2

Cycle 8: Idarubicin 10 mg/m^2 on day 1

Cycle 9: Carboplatin 900 mg/m^2 on day 1; thiotepa 3×15 mg/m^2 on days 1–3

Chemotherapy cycles were administered in three weekly-monthly periods, after having reached complete recovery of neutrophil and platelet counts (absolute neutrophil count, ANC >1.0 G/l, platelets >100 G/l). During the same period, the child also received multiple courses of either G-CSF (Neupogen; Amgen-Roche) or GM-CSF (Leucomax; Sandoz Schering-Plough) in order to abrogate chemotherapy-induced neutropenia (white blood cell count, WBC <0.8 G/l) and sepsis. G- and GM-CSF were administered once daily in a dose of 5 μg/kg as a subcutaneous injection for 5–10 days until the white blood cell count recovered (WBC >2.0 G/l). Growth factor selection was based on drug availability. GM-SCF was applied in seven treatment courses at a total cumulative dose of 5.35 mg, and G-CSF over three courses at a total cumulative dose of 2.3 mg. During chemotherapy and growth factor therapy, the patient was carefully monitored, and his physical condition, hematological parameters, and renal and liver functions were checked on a routine basis. We observed no acute clinical side effects of CSF administration and have not found any abnormality in his laboratory values that could have been attributed to CSF administration.

With the administration of the aforementioned chemotherapy cycles, a further partial response was achieved and stable disease was sustained until March 1993. While still on chemotherapy, the patient's neurological condition deteriorated in May 1993, which was consistent with radiologically observed tumor progression. Severe brainstem symptoms developed, with difficulties in swallowing, speaking, and walking. In July 1993 the patient's condition deteriorated rapidly. He received his last chemotherapy cycle, consisting of carboplatin and thiotepa (cycle 9), and had a fully recovered white blood cell count and normal peripheral blood cells. Two days after completing chemotherapy, the patient developed pneumonia and 6 days later septic neutropenia supervened, with a white blood cell count of 0.1–0.2 G/l. G-CSF administration was started immediately. Without white blood cell recovery after 5 days of G-CSF therapy, the patient died of respiratory failure 12 months after the initial diagnosis.

Autopsy Findings

Histological examination of the primary tumor verified the presence of a glioblastoma multiforme, originating from the pons, invading the cerebellum. The tumor contained several areas of necroses and hemorrhages. Histological examination of the bone marrow showed almost empty, hypocellular marrow spaces. Most of the remaining cells were atypical cells with a plasmacytoid appearance. Based on this picture, a preliminary postmortem histological diagnosis of plasmacytoma was established. (Fig. 1). Multiple nodules of undifferentiated plasma cells were found in abundance in the lungs (Fig. 2a) and hilar lymph nodes (Fig. 2b) as well. In order to determine the clonality of the lymphoplasmacellular infiltrates, immunostaining for kappa and lambda immunoglobulin light chains was performed. The presence of both kappa and lambda antigen-containing cells in all of the examined tissue samples indicated an oligoclonal/polyclonal accumulation and/or proliferation of plasma cells. (Fig. 3a,b)

DISCUSSION

Multiple myeloma has not been described in childhood, but solitary plasmacytoma and plasmacytosis may occur under extremely rare conditions. Especially unusual is the observed organ-infiltrating form of plasmacytosis in a child with a brain tumor [11]. Kepes et al. reported seven cases of young individuals with a special, chordoid type of meningeal tumors, which were surrounded by massive polyclonal peritumoral lymphoplasmacellular infiltrates. They explained the development of these infiltrates by the presence of some unknown antigenic or chemical stimulants produced by the meningiomas themselves. In these cases the patients developed systemic symptoms of Castleman syndrome, which could be attributed to the plasma cell proliferation (dysgamma-

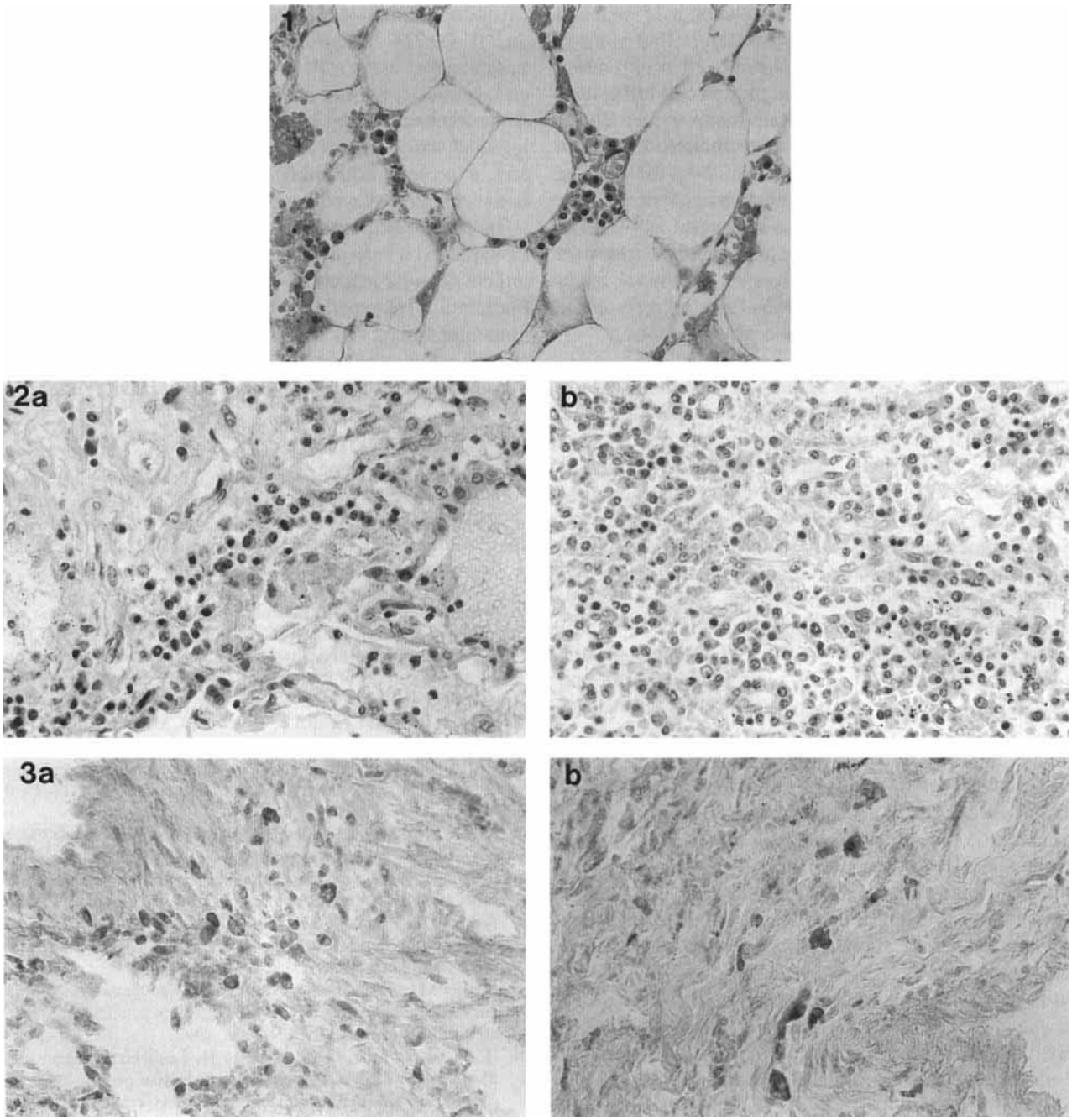

Fig. 1. Hypocellular bone marrow of patient infiltrated with undifferentiated plasmacytoid cells (H&E, original magnification ×200).
Fig. 2. Undifferentiated plasma cell infiltrates in the lung **(a)** and in a hilar lymph node **(b)** of the patient (H&E, original magnification ×200).
Fig. 3. Immunohistochemical staining of lung sections showing positivity for both kappa **(a)** and lambda **(b)** immunoglobulin light chains, indicating oligoclonal/polyclonal type of plasma cell infiltrates (original magnification ×200).

globulinaemia, growth retardation, hypochromic anemia). However, all of these children had the same unique type of brain tumor, and their clinical symptoms of plasmacytosis were already present at the time of diagnosis [12].

Other cases of meningiomas with conspicuous plasma cell components have been described earlier by Horten et al. In these patients, plasma cell proliferation/accumulation was confined to the brain tumor tissue and

its surroundings. One of the five patients, a 15-year-old girl, developed hypergammaglobulinaemia, but autopsy revealed no signs of systemic plasma cell proliferation [13]. In our patient, at autopsy no plasma cell infiltration was found around or inside the brain tumor tissue. Due to the fact that plasmacytosis was a postmortem finding in our case, no conclusions can be drawn about the possible presence of paraproteins or hypergammaglobulinemia in vivo. However, the patient never developed any clinical symptoms of plasma cell dyscrasia throughout the treatment period. Therefore, the possible role of a humoral factor derived from the tumor tissue seems to be unlikely in the development of the observed diffuse plasmacytosis.

Glioblastoma multiforme has been developed in a patient with IgD myeloma in remission, but this case too seems to bear little association with our case [14]. The possiblity of a second malignancy in our patient as a consequence of cytostatic therapy, however, cannot be completely excluded, although the type (plasmacytosis) and the timing (within the first year of chemotherapy) of its development would be very unusual [15]. Recently, rapid extramedullary spread of multiple myeloma has been described in two plasmacytoma patients following combination therapy with melphalan and GM-CSF. In these patients, multiple nodules of atypical plasma cells were found subcutaneously and in several internal organs. Extramedullary progression leading to death evolved in these cases, surprisingly, and parallel to an initially good response to therapy [16].

Interleukin-6 (IL-6 or B-cell stimulatory factor 2) is a known autocrine or paracrine growth factor for normal plasmablastic and myeloma cells as well [17]. Overexpression of IL-6 is characteristic for myeloma patients and is associated with aggressive disease and a poor prognosis [18]. GM-CSF has also been shown to stimulate myeloma cell proliferation in vitro, presumably by potentiating the response to IL-6 and increasing IL-6 expression in macrophages and fibroblasts [19,20]. It could be speculated that in the two myeloma patients GM-CSF therapy caused an increase in IL-6 expression, leading to the observed atypical disease progression. Not only has GM-CSF, but also G-CSF, has been shown to synergize with IL-6 to support myeloma cell proliferation. Its long-term application seems to be associated with pathogenic cell migration, causing the neutrophilic organ infiltration reported in a hairy cell leukemia patient [21].

On the basis of the observations described earlier, one may speculate that G- and/or GM-CSF may have contributed to the development of plasmacytosis in our brain tumor patient. The presumed mechanism of these changes might be extensive, repeated B-cell/plasma cell stimulation caused by CSFs and mediated, at least in part, by IL-6 overproduction, which could have resulted in plasmacytosis as a chronic reaction. However, the state of septic neutropenia itself is characterized by increased cytokine production and elevated levels of TNF, IL-1, and IL-6 [22]. Therefore, another possible explanation might be that in the state of sepsis, high concentrations of endogenous cytokines contributed to chronic plasma cell stimulation caused by exogenous G- and GM-CSF, leading to plamacytosis as an acute reaction. Other cytokines and, at present, still unknown cytokine network interactions may have played a role as well.

In conclusion, extensive growth factor support might have played a role in the development of a rare hematological disorder in a child with a glioma of the brainstem. Further clinical experience will define possible complications and limitations of the use of these agents. Based also on a few other reports in the literature, a more cautious application of growth factors may be suggested.

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